UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/601,997	12/15/2000	Jocelyn M Molony	119368-00021 / 2307US	5984

77202 7590 05/22/2009

K&L Gates LLP
3580 Carmel Mountain Road
Suite 200
San Diego, CA 92130

EXAMINER	
EPPS -SMITH, JANET L	

ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
05/22/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/601,997	MOLONY ET AL.	
	Examiner	Art Unit	
	Janet L. Epps-Smith	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9-14,58-73 and 75* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9-14,58-73 and 75* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3-30-2009 has been entered.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. Claims 9-14, 58-73 and 75 are presently pending.

Response to Amendments

Claim Rejections - 35 USC § 112

4. Claims 9-14, 58-73 and 75 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. (New Matter).

5. In the reply filed 03/30/2009, Applicants described the claimed invention as amended to comprise to render it clear that the method relies on the use of a family of oligonucleotides that are based on the sequence of a target nucleic acid molecule such that they are complementary to portions, but the complementary regions are distributed

throughout the target. Therefore, Applicants concluded that "[H]ence, not necessarily all of the oligonucleotides inhibit expression of the target gene." (see claim 58) However, Applicants have not provided any reference to the specification as filed to support their arguments and/or their amendments.

6. "[W]hen filing an amendment an applicant should show support in the original disclosure for new or amended claims. See MPEP § 714.02 and § 2163.06 ("Applicant should * * * specifically point out the support for any amendments made to the disclosure."). To comply with the written description requirement of 35 U.S.C. 112, para. 1, or to be entitled to an earlier priority date or filing date under 35 U.S.C. 119, 120, or 365(c), each claim limitation must be expressly, implicitly, or inherently supported in the originally filed disclosure. When an explicit limitation in a claim "is not present in the written description whose benefit is sought it must be shown that a person of ordinary skill would have understood, at the time the patent application was filed, that the description requires that limitation." Hyatt v. Boone, 146 F.3d 1348, 1353, 47 USPQ2d 1128, 1131 (Fed.Cir. 1998).

7. Furthermore, Applicants have inappropriately characterized the claimed invention, specifically wherein Applicants argue that the "complementary regions are distributed throughout the target." However, contrary to Applicant's assertions, "[t]he oligonucleotide family comprises a plurality of nucleic acid molecules; each member of the oligonucleotide family encodes a transcription product comprising a sequence that is complementary to a sequence contained in the mRNA transcribed from the sample nucleic acid sequence in the target nucleic acid molecule;" (see lines 10-13 of claim 58)

therefore the complementary sequences are located within the mRNA sequence encoded by the sample nucleic acid sequence comprised within the target nucleic acid sequence, and are not distributed throughout the target nucleic acid.

8. Additionally, Applicants have added new claim 75, which recites the range "about 20," again Applicants have not provided any reference to the specification or claims as originally filed to support this new limitation.

9. Applicant's amendment is therefore considered to introduce new matter into the disclosure since the specification as filed does not support Applicant's amendment to the claims as set forth above.

10. Applicant's arguments with respect to the rejection of claims 9-14 and 58-73 under 35 USC 112, 2nd ¶, as set forth in the prior Office Action, have been considered but are moot in view of Applicant's amendment and the new ground(s) of rejection set forth below.

11. Claims 9-14, 58-73, and 75 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

12. Claim 58, and those claims dependent therefrom, as set forth in the amendment filed 3-30-09 recites wherein: "[e]ach member of the oligonucleotide family encodes a transcription product comprising a sequence that is complementary to a sequence contained in the mRNA transcribed from the sample nucleic acid sequence in the target nucleic acid molecule;" (see lines 10-13 of claim 58). Claim 58 further recites wherein the "the sequences of the mRNA to which the transcription product of the family

members are complemenary (sp) are distributed throughout the target nucleic acid molecule." The claimed invention is again considered vague and indefinite since in one instance the claim recites wherein the transcription products of the oligonucleotides are complementary to the mRNA transcribed from the sample nucleic acid, and in another instance recites wherein the sequences of the mRNA to which the transcription products are complemenary (assuming complementary) are distributed throughout the target nucleic acid, and not limited to wherein the transcription products are complementary to the mRNA encoded by the sample nucleic acid comprised within the target nucleic acid.

13. Additionally Applicants have introduced the term "complemenary" into claim 58, this term appears to be spelled incorrectly, it is likely that Applicants intended the limitation to recite "complementary."

14. Claim 75 recites the phrase "about 20 members," since Applicants have not defined the breadth of the term "about" as recited in this phrase, one of ordinary skill in the art would not be able to ascertain the metes and bounds of the claimed invention.

Claim Rejections - 35 USC § 103

15. The rejection of claims 9-14, and 58-73, under 35 U.S.C. 103(a) as being unpatentable over Wagner et al. and Draper et al. (US 5,496,698) in view of Gudkov et al. (see PTO-892 of 02-03-2005), is withdrawn in response to Applicant's arguments.

Claim Rejections - 35 USC § 102

16. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

17. The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

18. Claims 9-14 and 58-73 and 75 are rejected under 35 U.S.C. 102(e) as being anticipated by Thompson (US Patent No. 6,448,009).

19. The instant claims are drawn to the following, as summarized by Applicants in the reply filed 03/30/2009 (see page 9 of 24, ¶ 1 of Applicant's reply):

"a high throughput method for assigning a function to a gene of unknown function by employing a library of a family of oligonucleotides based on a target gene, where sequences of the mRNA to which the transcription product of the oligonucleotide family members are complemenary are distributed throughout the target nucleic acid molecule such that among the members of the library are those that inhibit function of the target. *This does not require knowledge of the conformation or structure of the target gene, and as a result does not require any intermediate bacterial cloning steps nor any design steps.*

The use of the library of the family of oligonucleotides provides the oligonucleotide that will inhibit expression. As a result the method is amenable to a high throughput format. In addition, the method specifically requires that the oligonucleotides are provided in vectors that include means for directionality so that the double-stranded DNA is ligated into the delivery vector in the correct orientation for expression. The combination of teachings references does not teach or suggest such method."

Thompson, U.S. Patent No. 6,448,009 B1, at the abstract, cols. 3-7, 9-13, and 18-24, and Figure 7-8 discloses nucleic acid catalysts with one or two target binding domain arms designed to be random and that flank the catalytic domain, which are cloned into a retroviral vector to create a library of nucleic acid catalysts; the library is introduced into target cells; the cells with the desired characteristics are screened and selected, the nucleic acid catalysts from the desired cells are isolated, the sequence of the nucleic acid catalyst binding arms are determined, and the sequence information from the binding arms is used to isolate the nucleic acid molecules (e.g., genes) of interest using arm-specific capture probes (see Figures 6, 7, 8 and 10). Thompson, at. col. 6, line 66 to. col 7, states:

> Figure 7 is a diagram of a hammerhead ribozyme. The consensus hammerhead cleavage site in a target RNA is a "U" followed by "H" (anything but "G"). The hammerhead ribozyme cleaves after the "H". This simple di-nucleotide sequence occurs, on average, every 5 nt in a target RNA[.] Thus, there are approximately *400* potential hammerhead cleavage sites in a 2-Kb MRNA. Stems I and II are formed by hybridization of the hammerhead binding arms with the complementary sequence in target RNA; it is these binding arms that confer specificity to the hammerhead ribozyme for its target. The binding arms of the hammerhead are interrupted by the catalytic domain that forms part of the structure responsible for cleavage.
>
> FIG. 8 shows a scheme for the design and synthesis of a Defined Library: simultaneous screen of *400* different ICAM-targeted ribozymes is used as an example. DNA oligonucleotides encoding each ICAM-targeted ribozyme are synthesized individually (A), pooled (B), then cloned and converted to *retroviral vectors* as a pool. The resulting retroviral vector particles are used to transduce a target cell line that expresses ICAM (B). Cells expressing ribozymes that inhibit ICAM expression (ICAM-low) are sorted from cells expressing ineffective ribozymes by FACS sorting (C), effective ribozymes enriched in the ICAM-low population of cells are identified by filter hybridization (D).

Thompson at col. 8, lines 1-30, and Example 3, so. 19, line 59 to col. 20, line 31, used a ribozyme library introduced into human cells so as to select and identify

ribozymes from cells with altered phenotypes, after which the ribozymes from the selected cells were amplified. Thompson states:

> A Defined Ribozyme Library containing 40 different hammerhead ribozymes targeting PNP was constructed as described above (FIGS. 12-14). PNP is an enzyme that plays a critical role in the purine metabolic/salvage pathways. PNP was chosen as a target because cells with reduced PNP activity can be readily selected from cells with wild-type activity levels using the drug 6-thioguanosine. This agent is not toxic to cells until it is converted to 6-thioguanine by PNP. Thus cells with reduced PNP activity are more resistant to this drug and can be selectively grown in concentrations of 6-thioguanosine that are toxic to cells with wild-type activity levels.
>
> The PNP-targeted Defined Ribozyme Library expression vectors were converted into retroviral vector particles, and the resulting particles were used to transduce the Sup T1 human T cell line. A T-cell line was chosen for study because T lymphocytes are more dependent on the purine salvage pathway and thus are highly susceptible to 6-thioguanosine killing. Two weeks after transduction, the cell were challenged with 10 mmol 6-thioguanosine. Resistant cells began to emerge two weeks after initiation of selection. 6-Thioguanosine-resistant cells were harvested, and the ribozyme-encoding region of the expression vector was amplified using PCR and sequenced. The sequence pattern of the ribozyme region in the selected cells was significantly different from that produced from the starting library shown in Fig. 13. In the original library, sequences of the binding arms were ambiguous due to the presence of all 40 PNP-targeted ribozymes (FIG. 13). However, the sequence of the ribozyme-encoding regions from the 6-thioguanosine selected cells was clearly weighted towards one of the ribozymes contained in the original pool-the ribozyme designed to cleave at nucleotide #32 of PNP mRNA. These data suggests that the ribozyme targeting position 32 of the PNP mRNA appears to be more active than the other 39 PNP-targeted ribozymes included in the pool.

The teachings of Thompson clearly disclose a method involving the screening of a library of oligonucleotides which encode a transcription product that is complementary to a known or unknown target nucleic acid, wherein the disclosed methods allow one of skill in the art to assign a function to previously known or unknown gene. See the following description of Thompson, see col. 9-10:

> The method of the instant invention involves designing and constructing a catalytic nucleic acid library, where the catalytic nucleic acid includes a

catalytic and a substrate binding domain, and the substrate binding domain (arms) are randomized. This library of catalytic nucleic acid molecules with randomized binding arm(s) are used to modulate certain processes/attributes in a biological system. The method described in this application involves simultaneous screening of a library or pool of catalytic nucleic acid molecules with various substitutions at one or more positions and selecting for ribozymes with desired function or characteristics or attributes. This invention also features a method for constructing and selecting for catalytic nucleic acid molecules for their ability to cleave a given target nucleic acid molecule or an unknown target nucleic acid molecule (e.g., RNA), and to inhibit the biological function of that target molecule or any protein encoded by it.

It is not necessary to know either the sequence or the structure of the target nucleic acid molecule in order to select for catalytic nucleic acid molecules capable of cleaving the target in this cellular system. The cell-based screening protocol described in the instant invention (ie., one which takes place inside a cell) offers many advantages over extracellular systems, because the synthesis of large quantities of RNA by enzymatic or chemical methods prior to assessing the efficacy of the catalytic nucleic acid molecules is not necessary. ***The invention further describes a rapid method of using catalytic nucleic acid molecule libraries to identify the biological function of a gene sequence inside a cell.*** Applicant describes a method of using catalytic nucleic acid molecule libraries to identify a nucleic acid molecule, such as a gene, involved in a biological process; this nucleic acid molecule may be a known molecule with a known function, or a known molecule with a previously undefined function or an entirely novel molecule. This is a rapid means for identifying, for example, genes involved in a cellular pathway, such as cell proliferation, cell migration, cell death, and others. This method of gene discovery is not only a novel approach to studying a desired biological process but also a means to identify active reagents that can modulate this cellular process in a precise manner.

Thompson also describes the use of random ribozyme libraries, see the following:

By "Random Library" as used herein is meant ribozyme libraries comprising all possible variants in the binding arm (s) of a given ribozyme motif Here the complexity and the content of the library is not defined. The Random Library is expected to comprise sequences complementary to every potential target sequence, for the ribozyme motif chosen, in the genome of an organism. The Random Library can be a monomer or a multimer Random Library (see FIG. 17). By monomer Random Library is meant that one ribozyme unit with random binding arms. By multimer Random Library is meant that a transcription unit includes more than one ribozyme unit. The number of ribozyme units are preferably 2,3,4, 5, 6,7, 8,9, or 10. (see claim 66 and 75)

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Smith whose telephone number is 571-272-0757. The examiner can normally be reached on M-F, 10:00 AM through 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Janet L. Epps-Smith/
Primary Examiner, Art Unit 1633